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UNDERSTANDING THE PATHOGENESIS OF ALZHEIMER'S DISEASE

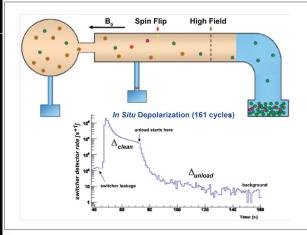
HEADS UP!

Los Alamos NATIONAL LABORATORY

Ultracold neutron accomplishments at LANSCE

The weak nuclear force is one of the four fundamental forces in nature, along with gravity, electromagnetism, and the strong nuclear force. Measuring the weak nuclear force parameters is one of the best ways to improve our fundamental understanding of the physics laws of the universe. Neutron beta decay provides one of the most accessible windows onto the weak nuclear force, enabling measurements at LANSCE with comparable precision to the Large Hadron Collider now starting operations at CERN, Switzerland.

The ultracold neutron (UCN) project is an ongoing effort to measure the asymmetry in the beta decay of the neutron better than any previous experiments. UCN are neutrons with energies low enough to undergo total external reflection from an effective potential energy barrier EFermi at some material surfaces, and thus can be stored in material bottles for experiments. The project uses polarized ultracold neutrons produced at LANSCE



A schematic of a test measurement of neutron depolarization. The experiment is shown as the circle on the left. The neutrons (depicted as dots) flow through the experiment and into a detector on the right. (Bottom): The graph shows a typical depolarization measurement, which traps depolarized neutrons in the experiment while cleaning out the properly polarized ones. Any depolarized neutrons would show up as a peak under the label Δ_{unload} . The number of detected depolarized neutrons was consistent with zero, with sufficiently high precision to show that depolarization will not limit the precision of the final project results.

because they offer systematic uncertainties smaller than and complementary to those of all previous experiments, which used cold neutron beams. In previous years, the project accumulated statistics for a 1% uncertainty on the decay asymmetry, which is comparable to the uncertainties on previous experiments. The ultimate goal of the project is to decrease the total uncertainty to about 0.25%. In order to do this, two things are necessary: a significant increase in the detected neutron decay rate over that seen in previous years, and measurement of the main sources of systematic uncertainty to prove that they are as low as originally thought.

Both of these goals were accomplished during 2009. The decay rate approximately doubled, compared to 2008, by improving the ratio of detected decays to incident ultracold neutrons. All the leading systematic uncertainties were studied and established to be sufficiently low to allow the ultimate goals of the project to be met. The leading systematic uncertainties are the depolarization of the neutrons in the experiment, the energy loss of the decay beta particles while they are detected, and the undetected backscatter of the decay beta particles

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Ultracold... from their detectors. All three of these effects were studied in depth during 2009. As a result of the engineering run during 2009, the UCNA project is positioned to achieve the world's best measurement of the neutron beta decay asymmetry during the next accelerator cycle in 2010. An additional 3 million decay events were detected at the higher rates needed for the statistics of the final measurement. The DOE Office of Science funds the research.

Technical contact: Frank Merrill

Andrey Kovalevsky and Suzanne Fisher recipients of Los Alamos Distinguished Postdoctoral Awards

The awards recognize individuals or small teams who have made an outstanding and unique contribution to the Lab's programmatic and scientific work during FY09. Their accomplishments display unusual creativity, innovation, or dedication.





Kovalevsky and Fisher (B-8) came to Los Alamos as a Director's Postdoctoral Fellow and a postdoctoral research associate, respectively. They received an award for the Protein Crystallography Station Team. The team is recognized for successfully running the Protein Crystallography Station (PCS) at the Lujan Center, as well as the effective application of x-ray and neutron crystallography to understand enzyme mechanisms related to three proteins.

The PCS is a neutron crystallography capability for the external structural biology community, funded by the Office of Biological and Environmental Research of DOE, and run by the Bioscience Division as part of the LANSCE user program. Kovalevsky and Fisher provided full scientific and technical coverage for the PCS, coordinated the peer review process, and scheduled beam time. In the absence of senior and more experienced scientists to carry out this work, the team took responsibilities beyond duty calls and provided the services. In addition to presenting seminars and posters. the team's works on understanding the mechanisms of three different enzymes resulted in a number of publications, several in top ranking journals such as the Journal of Molecular Biology, the Journal of American Chemical Society and the Journal of Medical Chemistry. Paul Langan (B-8) nominated them. The Deputy Director of the Lujan Center stated, "the scientific motivation and expertise of the two individuals is rarely found in other early career scientists."

Nuclear cross sections for accelerator production of a therapy isotope

Actiumum-225 (225Ac) has extraordinary potential for the treatment of metastatic cancer, and it is one of a few alpha emitters being considered for clinical trials. The isotope decays via four daughter isotopes, each yielding an alpha particle useful for local destruction of tumor sites. The alpha particles could destroy cancer cells while causing little damage to surrounding healthy tissue (e.g., alpha-immunotherapy). However, if brought into use, the demand for this isotope would greatly exceed the current national supply, which is from a single 150 mCi thorium-229 source harvested from uranium-233 by Oak Ridge National Laboratory many years ago. The National Institutes of Health and the Nuclear Science Advisory Committee have identified ²²⁵Ac as a critical isotope that requires additional production to address potential use in cancer therapy. Therefore, the DOE Office of Science is funding work at LANL to develop a proof of concept accelerator production process for this important isotope, using proton beams available at LANSCE in the Isotope Production Facility (IPF) and the Blue Room of the Weapons Neutron Research (WNR) facility.

Actinium-225 can be produced via proton-induced nuclear reactions on thorium-232 (²³²Th). Other nuclear reactions can also occur; therefore detailed knowledge of the proton energy-dependent cross-sections of all relevant nuclear reactions is needed to develop an accelerator based process to maximize the production of ²²⁵Ac and minimize the production of long-lived impurities.

| Pa 226 | Pa 227 38,3 m | Pa 228 22 h | Pa 229 | Pa 230 | Pa 231 | Pa 232 | Pa 233 |
|--|--|--|--|--|---|---|--|
| 6.86; 6,32 | α 6,466; 6,416 γ 65; 110 | ε; α 6,078; 6,105; 5,799; 6,118 γ 911; 463; 969; 965 | 6; a 5.58 5,670; 5,61 (119; 40; 144 e | 6: 8" 0.5 a 5.345; 5,326 y 952: 919: 455 | a 5.014; 4.952; 5.028 - Mail 701, 3.00, 303 e ⁻ e 200; er < 0.020 | η= 0 γ 969; 894 150 | 7312; 3 0; 341; 6 a 20+1; oj < 0; |
| Th 225 8,72 mg | Th 226 | Th 227 18,72 d | Th 228 1,913 a | Th 229 7880 a | Th 230 754 104 a | Th 231 25,5 h | Th 232 |
| 1 6,482; 6,445 6,504; 7 321; 246; 359; 306 | α 6,336; 6,230 γ111; (242; 131) θ | a 6,078; 5,978; 5,787 236; 50; 256 e~; \(\sigma 200\) | α 5.423; 5,340 γ 84; (216); α= Ο 20 σ 123 σ; < 0,3 | 31; e" σ=60, σ 30 | α.4,687; 4 9.1 γ(68; 11); e ⁻¹ Ne 2, σ 23,4 0,0005 | β= 0,3; 0,4 γ 26; 84 Θ | 1,405 1010 a a 4.013: 3.950: s y (64): e a 7.37: a,0.0000 |
| Ac 224 2,9 h | Ac 225 | Ac 226 29 h | Ac 227 21,773 a | Ac 228 6 3 h | Ac 229 62,7 m | Ac 230 122 s | Ac 231 7,5 m |
| 6.142; 6.060; 6.214 y 216; 132 | α 5,830; 5 5,732; γ 100; (1 188; 63); ε | β = 0,9; 1,1 ε; α 5,34 γ 230; 158; 254; 186 | β 0.04 α 4.953; 4.941 γ (100; 84 σ 880; σ 0,029 | α 4,27 ? γ 911; 969; 338; 965 | β ⁻ 1.1 γ 165; 569; 262; 146; 135 | β ⁻ 2.7 γ 455; 508; 1244 e ⁻ | β ⁻ γ 282; 307; 221; 186; 369 |
| Ra 223 11,43 d | Ra 224 3,66 d | Ra 225 | Ma 226 1600 a | Ra 227 42,2 m | Ra 228 5,75 a | Ra 229 4,0 m | Ra 230 93 m |
| a 5,7162; 5,6067 y 269; 154; 324 C 14; or 130; or 0,7 | α 5,6854; 5,4486 γ 241; C 14 σ 12.0 | β ⁻ 0.3; 0,4 γ 40 e ⁻ | α 4,7843; 4,601 γ 186; C 14 σ ~ 13 σ ₁ < 0.00005 | β ⁻ 1,3 γ 27: 300: 303 | β = 0.04, γ (14; 16) e = σ 36; σ ₁ < 2 | β ⁻ 1,8 | β ⁻ 0,8 γ 72; 63; 203; 470 e ⁻ |

Nuclear reactions of interest (red arrows) for the production of ²²⁵Ac in a thorium target. The blue arrows indicate decay from parent isotopes.

Scientists from Chemistry (C-IIAC and C-NR) and LANSCE (LANSCE-NS) divisions completed the first phase of measuring the nuclear cross sections for the accelerator production of ²²⁵Ac. The researchers irradiated ²³²Th foils with 800 MeV protons at LANSCE in the WNR facility, and then transported the foils to TA-48 for gamma counting and alpha assay. They dissolved one of

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Frank Valdez (C-IIAC) uses the remote manipulators at the Isotope Production Facility (LANSCE).

Isotope... of the thorium foils and separated the fractions by ion exchange for the alpha assay. This complex and time-critical portion of the experiment was executed in early December 2009. Since then, the foils and separated fractions have been subjected to continuous gamma and alpha assay to follow the decay of the actinide isotopes of interest as well as all of the co-produced fission products.

Despite the complexity of the spectra, it is clear that ²²⁵Ac is present among the nuclear reaction products. Ongoing data analysis focuses on de-convolving the spectra to quantify all of the contributing isotopes that were created in the 800 MeV beam and subsequent decay chains. Similar irradiations using the 100 MeV beam at IPF and a specially generated 200 MeV beam at WNR are planned for later this year. Complete data analysis will provide the first set of energy dependent cross-section measurements for this important set of nuclear reactions. Hong Bach, Mike Fassbender, George Goff, Meiring Nortier (lead), Wayne Taylor, Frank Valdez, and Laura Wolfsberg (C-IIAC); Mike Cisneros, Don Dry, Mike Gallegos, and Russ Gritzo (C-NR); Leo Bitteker, Aaron Couture, John Ullmann, and Steve Wender (LANSCE-NS) are involved in this work. The DOE Office of Science, National Isotope Program (Kevin John, LANL Program Manager; Wolfgang Runde, National Isotope Program Manager) supports the work. American Recovery and Reinvestment Act stimulus funding through DOE was provided to the LANL Isotope Program to investigate and enhance the isotope production capabilities for ²²⁵Ac.

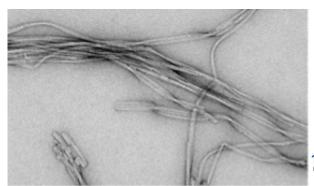
Understanding the pathogenesis of Alzheimer's disease

Alzheimer's disease is an irreversible, progressive brain disease that destroys memory and thinking skills, and eventually even the ability to carry out the simplest tasks. The brain develops abnormal clumps (amyloid plaques) and tangled bundles of fibers (neurofibril-

lary tangles) during the disease.

Amyloids are insoluble fibrous protein aggregates sharing specific structural traits. Abnormal accumulation of amyloid in organs may lead to amyloidosis, and may play a role in various other neurodegenerative diseases. One of the molecules which can form fibrous structures is the amyloid- β (A β) peptide. Its misfolding and aggregation has been linked to the pathogenesis of Alzheimer's disease. However, the driving forces and mechanism of A β aggregation in vivo remain unresolved.

 $\mbox{A}\beta$ molecules are amphipathic. That means they contain both hydrophilic (water loving) and hydrophobic (water hating) regions, which make them highly surface active.



100 nm

Transmission electron microscopy image of 25 micron A β fibrils obtained after the surface-adsorbed A β were re-introduced into the bulk and incubated for 5 days.

Jarek Majewski (LANSCE-LC) and collaborators (University of Chicago, University of New Mexico, University of Copenhagen, Gettysburg College, and Max-Planck Institute of Colloids and Interfaces) examined the effect of an idealized hydrophobic interface, the air/water interface, on the conformation, assembly state, and morphology of A β peptides partitioned to the interface. It is important to study A β 's interfacial dynamics at this interface to better understand the aggregation mechanism. The scientists used two surface-sensitive, complementary x-ray scattering techniques, grazing-incidence x-ray diffraction (GIXD) and x-ray reflectivity (XR), to resolve in situ angstrom-level details, and atomic force microscopy (AFM) to resolve micron-level organization of A β adsorbed at the air/water interface. Incubation experiments evaluated the effect of surface adsorbed A β to cause formation of fibrils.

Their research demonstrates that the A β spontaneously adsorb to the air/subphase interface to form a contiguous, single molecular film about 20 angstroms thick. The film contains approximately 100-angstrom sized ordered domains comprised of A β peptides

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HeadsUP!

When your body stays in same position for long periods of time, the same muscles do all the work all the time. Circulation through your body can me impaired. In addition, you may incur imbalanced muscle development as a result of using only part of your body to work.

Here are some ways to ensure you change postures frequently at work:

- Move your phone so you have to get up and stand while speaking.
- If you stand at work, move your phone so you can sit during the conversation
- If you have to type while you are on the phone use a speakerphone or get a headset.
- Do one simple stretch in between phone calls
- If you are fortunate to have a sit-stand work surface, work in the standing position for a few minutes every half hour.
- Place your computer printer in a location where you have to stand up versus using awkward reaches to retrieve documents.
- If you have snacks or beverages at work, place them far enough away so you have to get up in order to reach them.
- If you work with multiple documents, such as file folders, place them on a desk behind you and only keep about 15 minutes of work around you at a time. That way you have toget up every 15 minutes to get your next set of work. You may also break up tasks: copy15 minutes/type 30 min....
- Place your references far enough from your desk so you have to stand and reach them.
- Do not place heavy binders and books on the shelf directly over your desk. You may be tempted to reach for these items while you are seated.
- Use rest break software which is coming to ESD and will be free for all LANL computer users within the month of April!
 The ergonomics web page will provide all the information on the software when it is up and running.

Pathogenesis. . .folded in a β -sheet conformation. Thus, when the otherwise unfolded $A\beta$ partitions to the interface, the peptide misfolds into a conformation found in amyloid fibrils. This conformation propagates

over approximately 20 peptide molecules. The interface-driven misfolding and self-assembly of A β is observed at nano-molar peptide concentrations, far below the concentration at which A β aggregation occurs in bulk solution by homogeneous nucleation. The study shows that interface-adsorbed A β can seed fibril formation (see figure). This result indicates that interface-induced A β folding and self-assembly may serve as a heterogeneous nucleation controlled aggregation mechanism by which A β aggregates in vivo. Reference: "Amyloid- β Fibrillogenesis Seeded by Interface-induced Peptide Misfolding and Self-assembly," *Biophysical Journal* (in press). This work benefited from the use of the Lujan Neutron Scattering Center at LANSCE, which DOE's Office of Basic Energy Sciences funds.

Celebrating Service

Congratulations to the following MST employees celebrating service anniversaries this month:

John O'Donnell, LANSCE-NS

10 years



Published monthly by the Experimental Physical Sciences Directorate.

To submit news items or for more information,
contact Karen Kippen, EPS Communications,
at 606-1822, or kkippen@lanl.gov
LALP-10-020

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